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Three Times Weekly Tacrolimus Ointment Reduces Relapse in Stabilized Atopic Dermatitis: A New Paradigm for Use

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What's Known on This Subject

AD is the most common chronic, relapsing, inflammatory disease in children. Intermittent treatment with fluticasone propionate, a corticosteroid, plus standard-of-care emollients has been shown to reduce the recurrence of relapse more effectively than emollients alone.

What This Study Adds

For children with moderate to severe AD, initial corticosteroid use provided significantly better early relief than tacrolimus ointment alone. For children with stabilized moderate to severe AD, application of intermittent tacrolimus ointment to normal-appearing skin significantly reduced time to relapse compared with vehicle.

ABSTRACT

OBJECTIVE. Long-term, safe and effective therapeutic options for managing the chronic relapsing nature of atopic dermatitis are essential for improving patient quality of life. To minimize the risks of continued topical corticosteroid usage and potentially reduce the incidence of flares, we tested the efficacy and safety of a rotational paradigm of initial brief application of topical corticosteroid followed by long-term intermittent application of non-steroidal tacrolimus ointment to previously inflamed sites of dermatitis.

METHODS. In this 2-phase study, patients who were 2 to 15 years of age and had moderate to severe atopic dermatitis were randomly assigned to 4 days of twice-daily double-blind therapy with either alclometasone ointment 0.05% or tacrolimus ointment 0.03% (Phase I acute), followed by up to 16 weeks of twice-daily open-label tacrolimus ointment 0.03% (Phase I short-term). Patients whose disease stabilized underwent new randomization to double-blind tacrolimus ointment 0.03% or vehicle applied once daily, 3 times per week to clinically normal-appearing skin for up to 40 weeks (Phase II). Corticosteroid use was prohibited.

RESULTS. Of 206 randomly assigned patients, 152 completed Phase I; 105 of 152 were randomly assigned into Phase II (68 tacrolimus ointment and 37 vehicle). There were no differences in adverse events between alclometasone and tacrolimus (Phase I) or between tacrolimus and vehicle (Phase II). In the acute period, alclometasone-treated patients showed greater improvement in atopic dermatitis signs and symptoms; thereafter, when all patients applied tacrolimus ointment (short-term), there were no differences. In Phase II, tacrolimus-treated patients had significantly more disease-free days compared with vehicle, significantly longer time to first relapse, and significantly fewer disease relapse days.

CONCLUSIONS. For patients with stabilized moderate to severe atopic dermatitis, long-term intermittent application of tacrolimus ointment to normal-appearing but previously affected skin was significantly more effective than vehicle at maintaining disease stabilization, with a safety profile similar to vehicle. *Pediatrics* 2008;122:e1210–e1218

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This trial has been registered at www.clinicaltrials.gov (identifier NCT00106496).

Key Words

atopic dermatitis, tacrolimus ointment, intermittent dosing, topical calcineurin inhibitors, topical corticosteroids

Abbreviations

AD—atopic dermatitis
TCI—topical calcineurin inhibitor
PSGA—Physician's Static Global Assessment
%BSA—percentage of body surface area
CI—confidence interval

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ATOPIC DERMATITIS (AD), the most common chronic inflammatory skin disease in children, accounted for an estimated 7.4 million pediatric office visits between 1997 and 2004 in the United States.¹ This relapsing disease typically first manifests during early childhood, causing diminished quality of life and economic burden for children and their families.^{2–4} With no cure available, clinicians seek to provide patients with safe and effective interventions that maintain longer remission.

Topical corticosteroids are the mainstay of AD treatment; however, concerns of local and systemic effects limit their role in the long-term management of AD.^{5,6} Steroid-related adverse effects (eg, skin atrophy, striae, epidermal/

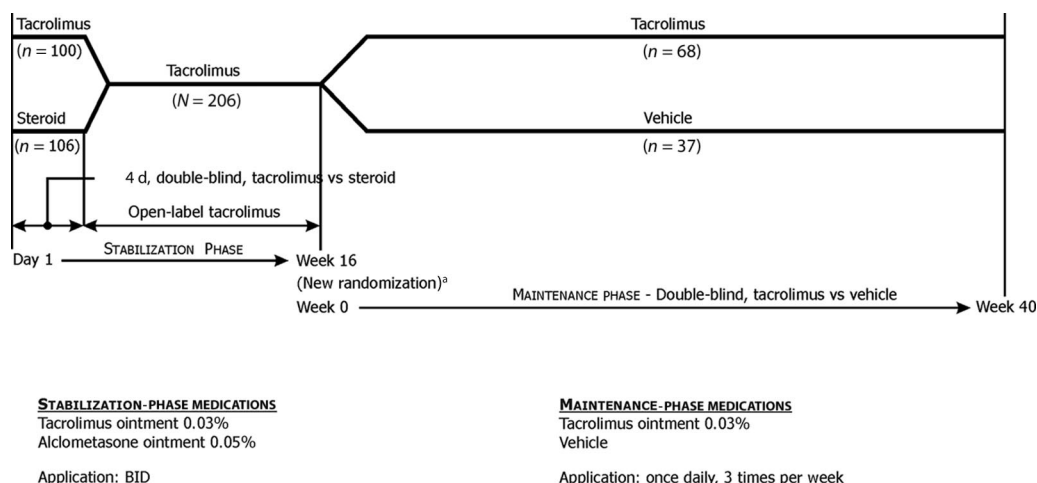


FIGURE 1

Study design. ^a New randomization of patients eligible (clear or almost clear) for continuation into maintenance phase.

dermal thinning) have not been observed with topical calcineurin inhibitors (TCIs), which are nonsteroidal agents.^{6–11} Twice-daily applications of tacrolimus ointment, a TCI, stabilizes moderate to severe AD in pediatric patients^{12–16}; is associated with long-term (1–4 years) safety and efficacy^{7–9,17}; and can be safely used on the face and eyelids, neck, and intertriginous regions.^{12,18,19}

To limit long-term application of topical corticosteroids, many clinicians calm the initial flare with a topical corticosteroid for a few days followed by several days of treatment with a TCI and then introduce intermittent application of a TCI to maintain control. This treatment approach, however, has not been formally tested. Intermittent application of fluticasone propionate cream, a midpotent corticosteroid,²⁰ has been shown to reduce the risk for disease relapse in pediatric patients with stabilized AD.²¹ Given the persistence of subclinical inflammation at sites of recurrent AD,²² we thus hypothesized that intermittent application of tacrolimus ointment to normal-appearing frequent flare sites might also reduce or prevent disease relapse. In this randomized, controlled study, we assessed the impact of initial treatment with a topical corticosteroid versus tacrolimus ointment on safety and efficacy and then tested the subsequent disease control with applications of tacrolimus ointment 3 times per week.

METHODS

Study Design and Patients

The study consisted of 2 distinct phases: stabilization (Phase I) and maintenance (Phase II; Fig 1). Stabilization consisted of 2 periods: acute double-blind treatment (4 days) in which patients were randomly assigned across all centers in a 1:1 ratio (tacrolimus ointment 0.03%: alclometasone ointment 0.05%) and patient numbers sequentially assigned, and short-term open-label treatment (up to 16 weeks) in which all patients received twice-daily tacrolimus ointment 0.03%. Although alclometasone, a low- to midpotency topical corticosteroid,²⁰ might not be the most efficacious choice for quelling moderate to severe AD, it was the preferred steroid

ointment formulation for facial application of the 2 products approved for use for pediatric patients with steroid-responsive dermatoses. The stabilization phase was preparatory for the main objective of the trial, to explore the effectiveness of intermittent therapy with tacrolimus ointment in reducing or preventing AD relapse. The stabilization phase also tested a secondary hypothesis that pretreatment with topical steroids reduces the potential for burning and stinging that may be experienced with tacrolimus ointment applications.

The maintenance phase was a 40-week, randomized, double-blind evaluation of tacrolimus ointment 0.03% or vehicle ointment applied once daily 3 times per week to previously affected sites. Eligible patients were randomly assigned across all centers in a 2:1 ratio (tacrolimus ointment:vehicle), and patient numbers were sequentially assigned. The study protocol was approved by institutional review boards at each site. All parents/legal guardians gave written informed consent before enrollment. Study design and methods have been described in detail elsewhere.²³

Boys or girls who were 2 to 15 years of age and had a diagnosis of AD (Hanifin and Rajka criteria²⁴) that was rated at least moderate (≥ 3) on the Physician's Static Global Assessment (PSGA) scale were eligible for randomization into the double-blind period of Phase I. Patients were not stratified according to disease severity. The PSGA is a standard 6-point scale of AD severity (0 = clear, 1 = almost clear, 2 = mild, 3 = moderate, 4 = severe, and 5 = very severe). Eligibility for the Phase I open-label period required application of study medication for a minimum of 6 times (over a minimum of 3 days) during the Phase I double-blind period. Achievement of a PSGA score of 0 ("clear") or 1 ("almost clear") during Phase I and treatment with open-label tacrolimus ointment until at least the week 2 visit of Phase I were required for randomization into Phase II.

Treatments

All study medications were labeled "for investigational use only." To preserve blinding during the double-blind

periods of Phase I and Phase II, we overlabeled the tubes of ointment with nonremovable labels and packaged them in identical boxes.

During the Phase I double-blind period, tacrolimus ointment 0.03% (Protopic [Astellas Pharma US, Inc, Deerfield, IL]) or alclometasone dipropionate ointment 0.05% (Aclovate [GlaxoSmithKline Consumer Healthcare, LLP, Pittsburgh, PA]) was applied twice daily for 4 days to all areas of active AD (Fig 1). Beginning with day 5, all patients applied open-label tacrolimus ointment 0.03% twice daily to all areas of active AD until at least the week 2 visit, even when the site(s) had become clear or almost clear. After the week 2 visit but for no longer than the week 16 visit, patients continued to apply tacrolimus ointment twice daily to all identified areas of AD until all sites were clear or almost clear. At this point, patients were eligible to enter Phase II. Patients were permitted to treat new lesions or lesions that had expanded after notifying the study investigator.

During Phase II maintenance, blinded tacrolimus ointment 0.03% or vehicle ointment was applied once daily, 3 times per week for up to 40 weeks (Fig 1) to the clinically normal-appearing skin of previous AD involvement (ie, all areas that were treated during Phase I, including areas that were added as a result of worsening of disease). Intermittent treatment was also permitted for new minor lesions (PSGA = 1). All relapses (PSGA ≥ 2) during Phase II were treated with open-label tacrolimus ointment 0.03% applied twice daily for up to a maximum of 8 weeks. Patients who did not restabilize (ie, PSGA still ≥ 2) during this 8-week period were discontinued from the study. Those who stabilized (PSGA 0 or 1) resumed their previously randomized regimen of blinded tacrolimus or vehicle ointment, applied to all areas treated at the beginning of Phase II as well as new treatment areas that were added during the disease relapse.

Corticosteroid use was prohibited for all patients throughout the study, except during the 4-day double-blind period of Phase I. Nonmedicated topical agents (including emollients) were permitted throughout the study (except on day 1 of Phase I) as long as they were applied at least 2 hours before or 2 hours after application of study treatment.

Study End Points

Phase I

In Phase I, the primary end point was the percentage of patients who reported cutaneous adverse events through week 2. Secondary end points included percentage of patients who reported cutaneous adverse events through day 4 and week 16, percentage of patients who were clear or almost clear by week 16, and percentage change from baseline in eczema area and severity index (EASI) score and percentage of body surface area (%BSA) affected. In addition, there was a patient assessment of itch based on a visual analog scale of 0 to 10 (0 = no itch and 10 = worst itch imaginable).

Phase II

The primary end point in Phase II was number of disease-free treatment days, defined as number of days between the start of maintenance treatment and the start of disease relapse treatment. Secondary end points in Phase II included time to first relapse, number of relapses per patient, number of relapse days, and severity of the worst disease relapse per patient.

Statistical Analysis

The efficacy population for Phase I included all randomly assigned patients who applied study drug at least once during Phase I and who had at least 1 postbaseline primary end-point visit. The efficacy population for Phase II included all randomly assigned patients who met the Phase II entry criterion of clear or almost clear during Phase I, applied study treatment at least once during Phase II, and had at least 1 postbaseline evaluation. The safety population was defined as all patients who applied study treatment at least once.

Baseline categorical data were analyzed using Fisher's exact test or χ^2 , as appropriate, and continuous data were analyzed with an analysis of variance. Between-treatment comparisons for continuous study end points were completed with an analysis of variance with treatment and geographic region as factors. Time to first disease relapse was analyzed by using Kaplan-Meier methods, and between-treatment differences were compared with a log-rank test. A Cochran Mantel-Haenszel test with region as the stratification variable was used to analyze the categorical data. All adverse events were coded via the MedDRA system. During Phase II, incidence rates of adverse events that occurred during double-blind treatment were summarized separately from those that occurred during open-label therapy for disease relapse. Treatment differences with $P < .05$ indicated statistical significance.

RESULTS

Study Patients

The study was conducted at 19 investigational sites within the United States; the first patient was randomly assigned in November 2004, and the last patient completed in July 2006. A total of 206 patients were randomly assigned to double-blind treatment in Phase I (106 received alclometasone followed by tacrolimus and 100 only tacrolimus). There were no differences between groups in baseline demographics, including disease severity ($P = .302$; Table 1). Of these 206 patients, 152 (80 alclometasone/tacrolimus and 72 tacrolimus only) completed Phase I (Fig 2). Of these 152 patients, 104 were clear or almost clear of disease: 62 (77.5%) of 80 in the alclometasone/tacrolimus group and 42 (58.3%) of 72 in the tacrolimus only group ($P = .01$).

A total of 105 (69%) patients were randomly assigned to Phase II, 68 to tacrolimus ointment and 37 to vehicle (Table 2); 1 patient who was randomly assigned to tacrolimus was found not to be clear or almost clear and was not included in any efficacy analyses. A total of 55 patients did not complete Phase II; the primary reasons

TABLE 1 Baseline Characteristics (All Randomly Assigned Patients)

Characteristic	Phase I		Phase II	
	Alclometasone Followed by Tacrolimus Ointment (n = 106)	Tacrolimus Ointment Only (n = 100)	Tacrolimus Ointment (n = 68)	Vehicle (n = 37)
Age, mean (SD), y	7.0 (3.9)	7.1 (4.0)	7.2 (3.8)	7.1 (4.1)
Gender, n (%)				
Female	64 (60.4)	50 (50.0)	37 (54.4)	22 (59.5)
Male	42 (39.6)	50 (50.0)	31 (45.6)	15 (40.5)
Race, n (%)				
White	44 (41.5)	49 (49.0)	31 (45.6)	15 (40.5)
Black	43 (40.6)	32 (32.0)	29 (42.6)	14 (37.8)
Hispanic	10 (9.4)	14 (14.0)	3 (4.4)	6 (16.2)
Asian	5 (4.7)	2 (2.0)	3 (4.4)	2 (5.4)
Other	4 (3.7)	3 (3.0)	2 (3.0)	0 (0.0)
Disease severity, n (%)				
Moderate	95 (89.6)	84 (84.0)	62 (91.2) ^{a,b}	33 (89.2) ^{a,b}
Severe	11 (10.4)	16 (16.0)	6 (8.8) ^{a,b}	4 (10.8) ^{a,b}
EASI score, mean (SD)	11.9 (7.9)	13.2 (9.0)	10.9 (7.6) ^b	10.4 (7.0) ^b
%BSA affected, mean (SD)	19.6 (17.8)	19.9 (18.0)	18.5 (18.5) ^b	14.2 (12.2) ^b
Itch score, mean (SD)	5.8 (2.4)	6.0 (2.5)	5.8 (2.4) ^b	6.6 (2.4) ^b

^a A patient's disease status was required to be clear or almost clear to be eligible for Phase II.

^b The values listed are the baseline measurements at the start of Phase I.

were voluntary patient withdrawal and loss to follow-up ($n = 34$; Table 2).

Efficacy

Phase I

Acute Double-blind Period (Days 1–4)

After 4 days of double-blind therapy, alclometasone-treated patients had a significantly greater percentage improvement from baseline in EASI score and %BSA affected than patients who were treated with tacrolimus ointment (Fig 3). Least-squares mean itch score decreased from 5.9 to 3.2 in the alclometasone group and

from 6.2 to 4.2 in the tacrolimus group ($P = .0009$). Few patients in either group achieved clear or almost clear status at the end of the 4-day treatment period, and the difference between groups was not significant (Fig 4). There was also no significant difference in the percentage of patients who improved by at least 1 PGA grade, and this lack of difference between groups continued through study end.

Short-term, Open-label Period

For all efficacy evaluations after the 4-day double-blind period, there were no differences between alclometasone and tacrolimus treatments (Fig 3), although

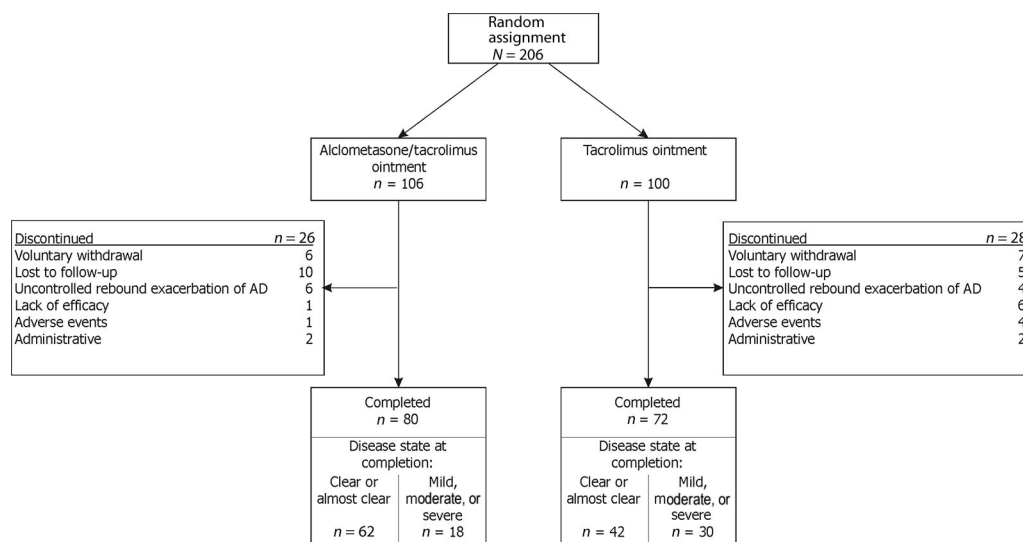


FIGURE 2
Patient disposition (Phase I).

TABLE 2 Patient Accounting (Phase II)

Patient Disposition	Tacrolimus Ointment	Vehicle
Randomly assigned	68	37
Assessable for safety ^a	68	36
Assessable for efficacy ^b	67	36
Completed, <i>n</i> (%)	39 (57.4)	11 (29.7)
Discontinued, <i>n</i> (%)	29 (42.6)	26 (70.3)
Lost to follow-up	8 (11.8)	6 (16.2)
Voluntary withdrawal	11 (16.2)	9 (24.3)
PSGA ≥ 2 after 8 wk open-label therapy	5 (7.4)	6 (16.2)
Lack of efficacy	1 (1.5)	0 (0.0)
Administrative	4 (5.9)	5 (13.5)

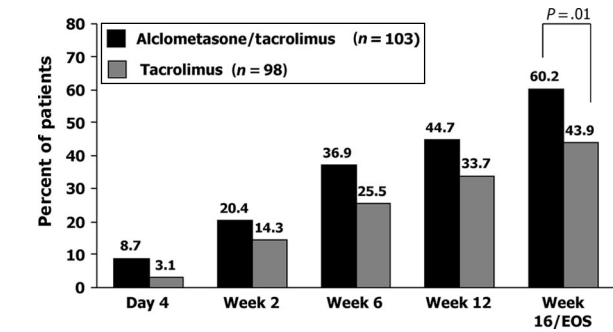
^a Included all patients who applied at least 1 application of study medication.

^b One patient was found not to have a PSGA of 0 or 1.

the percentage improvement in EASI score tended to be higher with alclometasone. The only exception was that significantly more patients in the alclometasone/tacrolimus group were clear or almost clear at week 16/end of study versus those in the tacrolimus group ($P = .01$; Fig 4).

Phase II

Tacrolimus-treated patients had a significantly greater number of disease-free treatment days compared with vehicle (mean: 174 days for tacrolimus vs 107 days for vehicle; $P = .0008$). Time (median) to first relapse was also significantly longer for patients who were treated with tacrolimus ointment compared with vehicle (116 days [95% confidence interval (CI): 56–188 days] for tacrolimus vs 31 [95% CI: 29–113 days] for vehicle; $P = .04$; Fig 5). Whereas the percentage of patients who experienced at least 1 disease relapse was similar between groups (72%), the mean number of disease relapse days was significantly less for tacrolimus (47 days) compared with vehicle (76 days; $P = .04$). Disease relapse treatment was successful in 90% (43 of 48) of tacrolimus-treated patients and in 77% (20 of 26) of vehicle-treated patients. There were no more than 3 relapses per patient in the tacrolimus group but up to 6 relapses per patient in the vehicle group. A total of 6.0%

**FIGURE 4**

Percentage of patients who achieved clear or almost clear status (Phase I). At week 16/end of study (EOS), there was a significant difference between the group that was initially treated with alclometasone and then switched to tacrolimus ointment versus the tacrolimus only group.

of tacrolimus-treated patients had 3 relapses during the course of the study compared with 19.4% of vehicle-treated patients who experienced 3 to 6 relapses during the study (Fig 6). Although the distribution of the worst severity of disease relapse did not differ statistically between treatments ($P = .20$), there were clinical differences; in the tacrolimus group, the severity of the worst relapse was mild in 67% and moderate in 31% of patients, whereas in the vehicle group, the worst relapse was mild in 46% and moderate in 54% of patients (Fig 7).

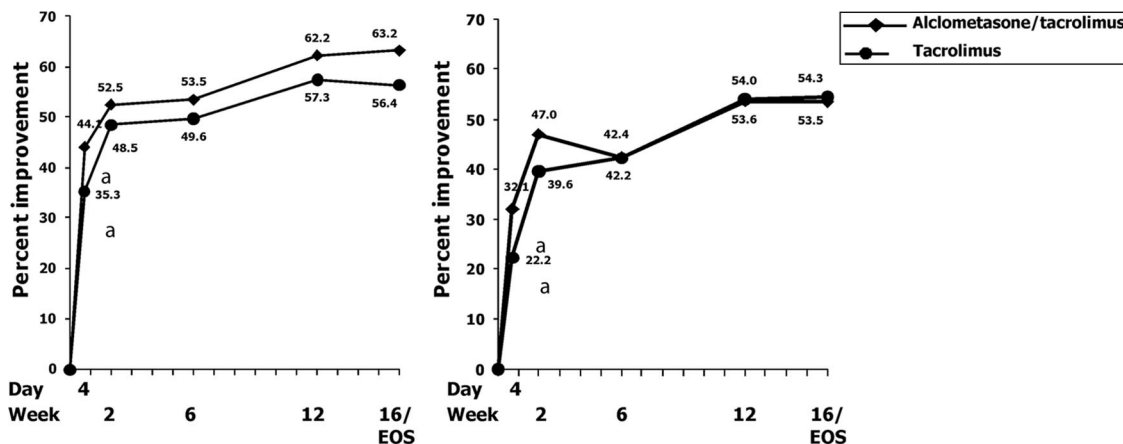
Safety

Phase I

There were no differences between treatments in application-site adverse events during Phase I, including the first 4 days in which patients applied either alclometasone or tacrolimus (Table 3). Application-site adverse events through week 2 were reported by 18% of patients in the tacrolimus group versus 21% in the alclometasone/tacrolimus group (Table 3).

Phase II

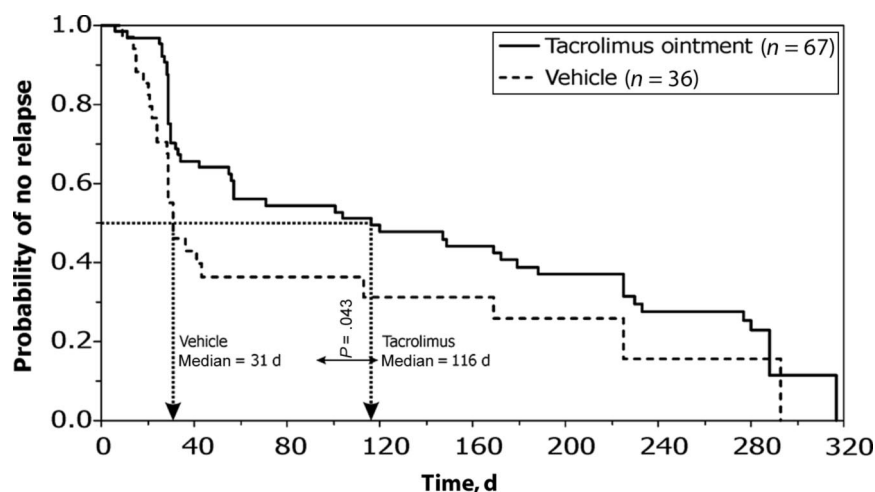
During Phase II (maintenance), the incidence of application-site adverse events was similar between treat-

**FIGURE 3**

Percentage improvement from baseline in EASI score ($^aP = .03$) and %BSA affected ($^bP = .02$). Values are least square means. EOS indicates end of study.

FIGURE 5

Kaplan-Meier plot of the probability of remaining free from relapse. The median time to first relapse was 116 days for tacrolimus versus 31 days for vehicle ($P = .04$).



ments (12% for tacrolimus vs 11% for vehicle; Table 4). Of the patients who received open-label tacrolimus ointment during the Phase II relapse periods, 5 (7%) of 74 patients experienced at least 1 cutaneous adverse event (Table 4).

DISCUSSION

Current AD relapse prevention strategies center on emollient use and avoidance of triggers. Long-term, intermittent (once daily, 3 times per week) applications of tacrolimus ointment to normal-appearing but recurrently affected skin of children with moderate to severe AD represents a new paradigm in relapse prevention. The data presented herein that support this new paradigm are a detailed subanalysis of the pediatric patients of a larger study that combined adult and pediatric patients with stabilized AD.²³ Time to first disease relapse was 4 times longer with intermittent tacrolimus ointment compared with vehicle, and, at most, 3 relapses per patient occurred in the tacrolimus group compared with 6 per patient in the vehicle group. The majority of tacrolimus-treated patients with disease relapse showed mild disease, whereas vehicle-treated patients who relapsed showed moderate disease involvement in >50% of episodes. Patients were permitted to use standard topical hydration therapy (emollients, creams, lotions)

throughout the trial; however, corticosteroid use was prohibited for all patients after the Phase I acute double-blind treatment period. Thus, the overall 85% success rate observed after treatment of disease relapse is attributed to monotherapy with twice-daily applications of tacrolimus ointment.

More than two thirds of the 152 patients with moderate to severe AD achieved clear or almost clear status by 16 weeks. Patients who were treated with alclometasone had significantly greater improvement in EASI score and %BSA at 4 days (but not by 16 weeks) than patients who were treated initially with tacrolimus ointment (Fig 3). Initial application of alclometasone, however, led to a significantly greater percentage of patients' achieving clear or almost clear status (Fig 4) at 16 weeks, despite the 15.5 subsequent weeks of tacrolimus monotherapy. The improved outcome with just 4 days of alclometasone supports the proposed paradigm. Nevertheless, it is possible that the trend toward milder baseline severity in alclometasone-treated versus tacrolimus-treated patients, despite not being statistically significant ($P = .302$), contributed to the results observed.

In previous studies that directly compared topical corticosteroids and tacrolimus ointment for pediatric patients with moderate to severe AD, application-site adverse events in the first few days of therapy (days 1–4)

FIGURE 6

Number of disease relapses. In the tacrolimus group, there was a maximum of 3 relapses per patient; in the vehicle group, the maximum was 6 relapses per patient. A total of 79% of patients in the tacrolimus group had 0 to 1 relapses compared with 64% of patients in the vehicle group. Distribution of tacrolimus vs vehicle relapses ($P = .06$).

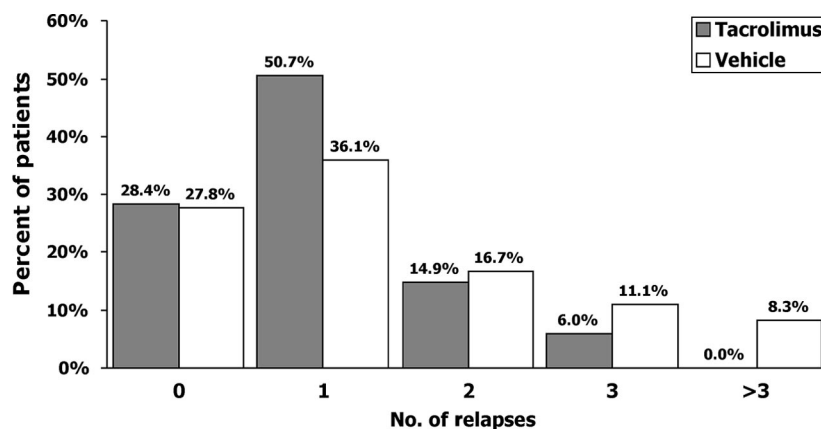
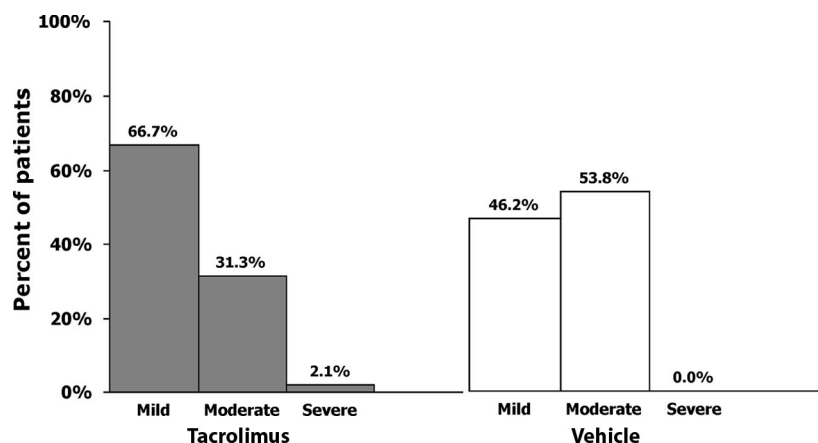


FIGURE 7

Distribution of worst severity of disease relapse. There was a more clinically favorable distribution in the tacrolimus group in the severity of the worst disease relapse (tacrolimus: mild disease 67%, moderate disease in 31%; vehicle: mild disease 46%, moderate disease 54%).



were significantly greater in the tacrolimus group, but thereafter the prevalence was comparable.^{13,16} The decrease in cutaneous events after the first week or 2 of therapy has been thought to relate to skin healing.^{12,13,16} Unlike previous reports,^{13,16} the incidence of burning and stinging in the first days of therapy in our study were no less in alclometasone-treated patients than in tacrolimus-treated patients.

The overall incidence of cutaneous events with intermittent application of tacrolimus was low and similar to vehicle and did not increase with prolonged intermittent tacrolimus ointment treatment. Likewise, long-term studies (1–4 years) of >5000 pediatric patients with active disease have demonstrated the safety of tacrolimus ointment when applied twice daily,^{7–9,17} and shorter term clinical and pharmacokinetic studies have shown that tacrolimus ointment is minimally absorbed.^{12,13,25–27} An integrated analysis of tacrolimus blood concentrations from pediatric clinical trials that evaluated twice-daily applications of tacrolimus ointment 0.03% and included 738 samples found that 99% of samples were <1 ng/mL and 95% were <0.5 ng/mL.²⁵ Current prescribing information (revised January 2006) for TCIs

(tacrolimus ointment and pimecrolimus cream) does not recommend continuous long-term use of these agents or application to areas of noninvolved skin; our results provide new data on the safety and efficacy of tacrolimus ointment for pediatric patients who had stabilized AD and applied the drug intermittently for up to 40 weeks in this manner. A recent preliminary review of the ongoing prospective pediatric longitudinal evaluation study (APPLES), which has enrolled >2800 children with a history of AD and previous treatment with tacrolimus ointment, found a low incidence of serious events (primarily infection and asthma), none of which has been attributed by study investigators to tacrolimus ointment, and no reports of malignancy since study enrollment.²⁸

In both phases of our study and for all treatments, the primary reasons for study discontinuation were voluntary withdrawal and loss to follow-up. In Phase I, 26% of patients discontinued from the 16-week study period, and in Phase II (40 weeks), 43% of tacrolimus-treated patients and 70% of vehicle-treated patients discontinued early. These percentages are consistent with dropout rates in the trial of intermittent application of fluticasone cream to pediatric AD patients, an approximate 6.5% withdrawal rate in the 4-week open-label treatment pe-

TABLE 3 Adverse Events (Phase I)

Application-Site Adverse Event, No. of Patients (%)	Double-Blind, Day 4		Open-Label Tacrolimus, Week 2	
	Alclometasone Ointment (n = 103)	Tacrolimus Ointment (n = 98)	Alclometasone/Tacrolimus ^a Ointment (n = 103)	Tacrolimus Ointment (n = 98)
Overall	13 (12.6)	14 (14.3)	22 (21.4)	18 (18.4)
Burning	9 (8.7)	9 (9.2)	10 (9.7)	12 (12.2)
Pruritus	4 (3.9)	6 (6.1)	10 (9.7)	6 (6.1)
Skin infections	0 (0.0)	1 (1.0)	0 (0.0)	3 (3.1)
Increased irritation (NOS)	1 (1.0)	0 (0.0)	1 (1.0)	0 (0.0)

Assessable population, which excluded 5 randomly assigned patients who took at least 1 dose of study medication but did not have a valid postbaseline visit. The total number of patients listed for overall application-site event may be less than the total of the individual events, because each patient may have had an event in >1 category. NOS indicates not otherwise specified.

^a This is the group that applied corticosteroid treatment during the double-blind period. All patients (N = 201) received open-label tacrolimus beginning with day 5 of Phase I.

TABLE 4 Adverse Events (Phase II)

Application-Site Adverse Event, No. of Patients (%)	Double-Blind Maintenance Periods		Relapse Periods
	Tacrolimus Ointment (n = 68)	Vehicle (n = 36) ^a	Tacrolimus Ointment (n = 74)
Overall	8 (11.8)	4 (11.1)	5 (6.8)
Burning	2 (2.9)	1 (2.8)	2 (2.7)
Pruritus	1 (1.5)	2 (5.6)	0 (0.0)
Skin infections			
Folliculitis	0 (0.0)	0 (0.0)	1 (1.4)
Molluscum	0 (0.0)	1 (2.8)	0 (0.0)
Other (NOS)	1 (1.5)	0 (0.0)	0 (0.0)
Increased irritation (NOS)	1 (1.5)	0 (0.0)	0 (0.0)
Application-site reaction (NOS)	1 (1.5)	0 (0.0)	0 (0.0)

NOS indicates not otherwise specified.

^a One randomly assigned patient did not apply study treatment and was not included in the safety population.

riod, and a withdrawal rate of ~25% for fluticasone and 78% for vehicle in the continuing 20-week double-blind period.²¹

Incorporating TCIs into a rotational treatment plan that includes topical corticosteroids occurs routinely in clinical practice, and we found that initial treatment with a corticosteroid provides significantly better early relief of the signs and symptoms of AD in pediatric patients with moderate to severe AD than tacrolimus ointment. Furthermore, once stabilized, long-term, intermittent (once daily, 3 times per week) applications of tacrolimus ointment to recurrently affected areas provides significantly more disease-free days compared with vehicle and a significantly longer time until first disease relapse, with a safety profile similar to that of vehicle. Our findings substantiate current clinical practice in the early treatment of AD and provide additional insight into a long-term strategy of disease control for pediatric patients with stabilized moderate to severe AD.

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Three Times Weekly Tacrolimus Ointment Reduces Relapse in Stabilized Atopic Dermatitis: A New Paradigm for Use

Amy S. Paller, Lawrence F. Eichenfield, Robert S. Kirsner, Toni Shull, Eileen Jaracz, Eric L. Simpson and for the US Tacrolimus Ointment Study Group

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